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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,369	04/20/2005	Andreas Axen	PU0284	4270

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EXAMINER	
FOSTER, CHRISTINE E	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,369	AXEN ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-13 and 26-28* is/are pending in the application.

4a) Of the above claim(s) *1-3,6-11 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/20/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of ***in vitro* methods** in the reply filed on 5/30/08 is acknowledged.

2. Claims 26-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/30/08.

3. Claims 1-3, 6-13, and 26-28 are pending in the application. Claims 1-3 and 6-11 were previously withdrawn from consideration pursuant to the restriction requirement mailed 10/12/07. Accordingly, claims 12-13 are subject to examination below.

Priority

4. The present application was filed on 4/20/05 and is a national stage (371) entry of PCT/SE03/01435, filed 9/12/03. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 0203226-6, filed on 10/31/2002 in Sweden.

Information Disclosure Statement

5. Applicant's Information Disclosure Statement filed 4/20/05 has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

7. The disclosure is objected to because of the following informalities:

8. There is a typographical error in the word "fulfill" on page 7, penultimate paragraph.

9. The specification at page 13, last paragraph discloses a "purified polypeptide consisting of a portion of a human IgG **heavy chain** starting at one of amino acids 106 to 128 and ending at one of amino acids 215 to 225 of human IgG **light chain** as set forth in SEQ ID NO:2" (emphasis added). Clarification and/or correction are requested as it is unclear how a single polypeptide (SEQ ID NO:2) could be both a heavy chain and a light chain.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

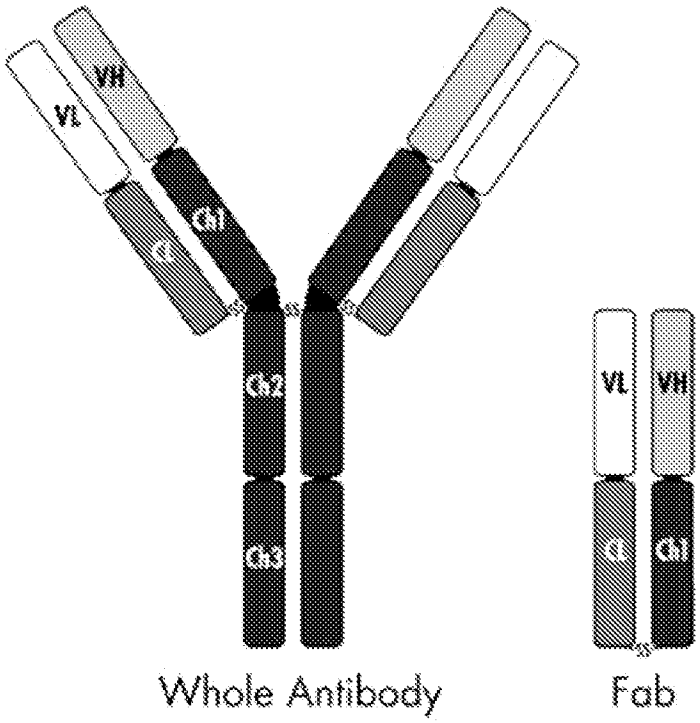
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a screening method for assessing the ability of chemical entities in a library to bind to a human κ-Fab constant part-comprising composition. This composition is a composite polypeptide that includes two polypeptide chains: a chain consisting of a portion of an IgG κ light chain, and a chain apparently consisting of a portion of an IgG heavy chain (see rejection under 112, 2nd paragraph below). More particularly, the first polypeptide chain corresponds to the first constant domain of the light chain (the CL domain), without the variable VL domain. The second polypeptide chain corresponds to the first constant domain of the heavy chain (the CH1 domain), without the variable VH domain. See also the instant specification at pages 2-3 and 7-8.

Therefore, in reference to the figure below, the claimed composition consists of the CL and CH1 domains of a particular antibody--a modified Fab fragment that lacks the variable VL and VH domains (the figure that follows was adapted from Wheeler et al., "Intrabody and Intrakine Strategies for Molecular Therapy", Molecular Therapy Vol. 8, No. 3, September 2003, pages 355-366, see page 356, Figure 1A).



In other words, the claimed composition corresponds to the lower half of the Fab fragment depicted above at right, a CL-CH1 heterodimer. While Applicant has clearly identified the desired structures of the genus of polypeptide compositions by reference to specified amino acid sequences, it is apparent that the claimed screening methods require the composition to have certain functional characteristics.

In particular, as disclosed instantly, the nature of the invention relates to a binding pocket that is at the interface of the CL and CH1 domains in a Fab fragment (specification, pages 11-13).

Therefore, assessment of binding to the composition as claimed would require that the two polypeptides of the composition *associate with each other* to form this binding pocket. It is noted that the instant claims do not specify or require that the two polypeptides of the composition be bound to each other in any way. The claims would therefore read on

compositions in which the two polypeptides are bound to each other, as well as compositions in which there is no association or binding between these molecules.

Since the disclosed methods have the goal of identifying compounds that would bind to the binding pocket, and because the binding pocket would only be present if the CL and CH1 domains were in association with each other, it appears that Applicant intends that the two polypeptides (CL and CH1 domains) would be bound to each other as a heterodimer.

Given this explicit focus on the binding pocket formed by the interface of these domains, the specification fails to convey evidence of possession of methods of assessing binding of chemical entities to polypeptide compositions in which the two polypeptides do not associate with each other (and hence where the binding pocket would not be present in the composition). See also the rejection under 112, 2nd paragraph below for omission of essential structural relationship.

Even assuming that Applicant intends that the two polypeptides be bound to each other in the composition, however, it is found that the specification fails to adequately describe such compositions.

Although the desired sequences of the polypeptide chains are identified, the prior art recognized unpredictability in producing recombinant antibody fragments; and the specification does not disclose methods of making the claimed fragments. Rather, all of the examples in the specification relate to intact Fab fragments that still contain the variable VL and VH domains.

Methods for producing such intact Fab fragments were known in the art at the time of filing; however, methods for producing antibody fragments consisting of only the CL and CH1 domains (without the Fab variable domains) were not.

The specification suggests that the claimed Fab fragment compositions can be produced according to standard procedures (pages 15-16), although no data are provided to indicate that the claimed compositions were actually produced. In particular, the specification suggests methods analogous to those reported by Mertens et al. and Schoonjans et al. (page 16, first paragraph).

However, the publication by Mertens et al. mentioned in the specification reports experiments in which attempts were made to produce Fab fragments that contained only CL-CH1 heterodimers, but these attempts were *unsuccessful*. In particular, Mertens et al. report that in mammalian cells, no product was produced when CL and CH1 domains were co-expressed. See Mertens et al. ("New recombinant bi- and trispecific antibody derivatives" In: Novel Frontiers in the Production of Compounds for Biomedical Use (Van Broekhoven, A, Shapiro, F, Anné, J, eds.), Focus on Biotechnology, Vol. 1, Dordrecht, Kluwer Academic Publishers, pp. 195-208, 2001, in particular the abstract; page 199, first paragraph; the paragraph bridging pages 201-202; and Figure 2B). Mertens et al. conclude that interaction between the CL-CH1 polypeptides to form a heterodimer depends on the presence of the VL and VH domains that are present in extended Fab fragments (pages 200-201).

Similarly, Mertens et al. (US 2004/0220388 A1) attempted to produce CL and CH1 domains as a heterodimer, co-expressing these molecules in eukaryotic cells [0051]-[0053]. As above, there was no detectable production of the heterodimer [0051]. Even when these two polypeptides were co-expressed along with their corresponding longer, extended counterparts (containing the variable domain of the Fab fragments), no secreted heterodimers could be detected (ibid and [0053]). Mertens et al. conclude that "[t]here was no detection of

heterodimeric protein unless the complete [light] chains were co-transfected with the complete Fd chains to form a Fab fragment" (see [0052]; the Fd fragment includes both the CH1 and VH regions of the heavy chain). Mertens et al. also indicate that their results are in agreement with those of other groups [0053].

Similarly, the article by Schoonjans et al. mentioned in the specification teaches that:

> The failure of the CL and CH1 domains to drive heterodimerization in mammalian cells when either the VL or the VH domain is removed from the Fab-chains (CL:Fd and CH1:L) suggests that interaction of the complete Fab chains is necessary to obtain heterodimers.

See Schoonjans et al., Biomolecular Engineering 17 (2001) 193–202, in particular at page 196, right column.

The teachings of Mertens et al. and Schoonjans et al. indicate that contrary to the suggestion in the disclosure, these standard methods of producing antibody fragments are not in fact methods of making the claimed composition, since they were actually unsuccessful in producing CL-CH1 heterodimeric compositions lacking Fab variable regions.

In addition, the instant claims encompass a genus of compositions, in which the two polypeptides may vary in length at both the N- and C-terminus. In disclosing only examples involving intact Fab fragments that include variable domains, Applicant has not disclosed any methods of making any compositions within the claimed genus. Moreover, Peteterson et al. ("Monoclonal Antibody Form and Function: Manufacturing the Right Antibodies for Treating Drug Abuse" The AAPS Journal 2006; 8 (2) Article 43, pages E383-E390, retrieved from http://www.aapsj.org) discuss that production of other types of antibody fragments (such as Fab and scFv fragments) was known in the art, but teach that:

> Each mAb and mAb form is a unique protein with distinct folding requirements as well as unique biochemical and biophysical characteristics that affect its ability to be expressed at high levels as a soluble, biologically active protein. To date, no single expression system appears ideal for the production of mAb or engineered mAb fragments.

See page 385, left column. Such teachings indicate variability within the claimed genus, as well as unpredictability associated with the production of antibodies and their fragments.

In summary, there is evidence of unpredictability in the art regarding successful production of antibody fragments, in that other groups tried and failed to produce Fab compositions containing only the CH1 and CL regions when using the methods suggested in the specification. Absent any disclosed methods of making the currently claimed compositions, the specification fails to convey evidence of possession of the recited compositions and in turn, of methods of using the compositions in methods for evaluating binding.

12. Claims 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention relates to the identification of a potential binding pocket in the three-dimensional structure of κ-type Fab fragments, which was identified through molecular modeling techniques (see Example 1).

The claims are directed to a screening method for assessing the ability of chemical entities in a library to bind to a human κ-Fab constant part-comprising composition. As discussed above, this composition is a composite polypeptide that includes two polypeptide

chains: a chain consisting of a portion of a IgG κ light chain, and a chain apparently consisting of a portion of an IgG heavy chain (see rejection under 112, 2nd paragraph below). More particularly, the first polypeptide chain corresponds to the first constant domain of the light chain (the CL domain), without the variable VL domain. The second polypeptide chain corresponds to the first constant domain of the heavy chain (the CH1 domain), without the variable VH domain. In other words, the composition is a modified Fab fragment that includes only the CL and CH1 domains but lacks the variable VL and VH domains that are part of Fab fragments.

Regarding the breadth of the claims, it is noted that the instant claims do not specify or require that the two polypeptides of the composition be bound to each other in any way. The claims would therefore read on compositions in which the two polypeptides are bound to each other, as well as compositions in which there is no association or binding between these molecules.

However, as disclosed instantly, the claimed methods are intended to identify chemical entities that bind to the binding pocket that is at the interface of the CL and CH1 domains in a Fab fragment (specification, pages 11-13). Assessment of binding to the composition would require that the two polypeptides of the composition *associate with each other* in a heterodimer in order to form such a binding pocket. The specification therefore fails to teach the skilled artisan *how to use* compositions that contain the two polypeptides in unbound form--because the binding pocket would only be present if the CL and CH1 domains were in association with each other, it is unclear how unassociated polypeptides could be used to identify compounds that would bind to the binding pocket.

Regarding production of the heterodimeric CL-CH1 compositions (where the two constant regions do interact with each other to form a potential binding pocket), the prior art teaches methods for producing various antibody fragments, for example using mammalian cells or *E. coli* expression systems (cytoplasmic or periplasmic expression). See discussion in Carter et al., U.S. 5,648,237, at columns 1-6. However, methods of producing antibody fragments consisting of only the CL and CH1 regions were not routine in the art.

The specification does not provide any working examples of the claimed invention, since in all of the disclosed embodiments, entire Fab fragments that contained the variable VL and VH domains were employed.

The specification suggests that the claimed Fab fragment compositions can be produced according to standard procedures (pages 15-16). In particular, the specification suggests methods analogous to those reported by Mertens et al. and Schoonjans et al. (page 16, first paragraph).

However, the publication by Mertens et al. mentioned in the specification reports experiments in which attempts were made to produce Fab fragments that contained only CL-CH1 heterodimers, but these attempts were unsuccessful. In particular, Mertens et al. report that in mammalian cells, no product was produced when CL and CH1 domains were co-expressed. See Mertens et al. ("New recombinant bi- and trispecific antibody derivatives" In: Novel Frontiers in the Production of Compounds for Biomedical Use (Van Broekhoven, A, Shapiro, F, Anné, J, eds.), Focus on Biotechnology, Vol. 1, Dordrecht, Kluwer Academic Publishers, pp. 195-208, 2001, in particular the abstract; page 199, first paragraph; the paragraph bridging pages 201-202; and Figure 2B). Mertens et al. conclude that interaction between the CL-CH1

polypeptides to form a heterodimer depends on the presence of the VL and VH domains that are present in extended Fab fragments (pages 200-201).

Similarly, Mertens et al. (US 2004/0220388 A1) attempted to produce CL and CH1 domains as a heterodimer, co-expressing these molecules in eukaryotic cells [0051]-[0053]. As above, there was no detectable production of the heterodimer [0051]. Even when these two polypeptides were co-expressed along with their corresponding longer, extended counterparts (containing the variable domain of the Fab fragments), no secreted heterodimers could be detected (ibid and [0053]). Mertens et al. conclude that "[t]here was no detection of heterodimeric protein unless the complete [light] chains were co-transfected with the complete Fd chains to form a Fab fragment" (see [0052]; the Fd fragment includes both the CH1 and VH regions of the heavy chain). Mertens et al. also indicate that their results are in agreement with those of other groups [0053].

Similarly, the article by Schoonjans et al. mentioned in the specification teaches that:

> The failure of the CL and CH1 domains to drive heterodimerization in mammalian cells when either the VL or the VH domain is removed from the Fab-chains (CL:Fd and CH1:L) suggests that interaction of the complete Fab chains is necessary to obtain heterodimers.

See Schoonjans et al., Biomolecular Engineering 17 (2001) 193–202, in particular at page 196, right column.

The teachings of Mertens et al. and Schoonjans et al. indicate that contrary to the suggestion in the disclosure, these standard methods of producing antibody fragments would not be successful in producing the CL-CH1 heterodimeric compositions required by the currently claimed methods. Therefore, the guidance of a general nature in the specification is insufficient

and would not predictably enable one of ordinary skill in the art to produce the claimed compositions.

In addition, the instant claims encompass a genus of compositions, in which the two polypeptides may vary in length at both the N- and C-terminus. However, Peteterson et al. ("Monoclonal Antibody Form and Function: Manufacturing the Right Antibodies for Treating Drug Abuse" The AAPS Journal 2006; 8 (2) Article 43, pages E383-E390, retrieved from http://www.aapsj.org) discuss that production of other types of antibody fragments (such as Fab and scFv fragments) was known in the art, but teach that:

> Each mAb and mAb form is a unique protein with distinct folding requirements as well as unique biochemical and biophysical characteristics that affect its ability to be expressed at high levels as a soluble, biologically active protein. To date, no single expression system appears ideal for the production of mAb or engineered mAb fragments.

See page 385, left column. Such teachings indicate unpredictability associated with the production of antibodies and their fragments, in that each molecule behaves differently. Consequently, one cannot extrapolate the teachings of the specification (involving intact Fab fragments) to the scope of the claims (involving CH1-CL fragments without the variable regions) because said teachings represent insufficient guidance and objective evidence to predictably enable the use of the claimed invention.

In summary, due to the state of the prior art, which teaches that the disclosed methods would not be successful in the claimed compositions (containing only the CL and CH1 constant regions of Fab fragments in association with each other to form a binding pocket), and when taken together with the unpredictability associated with the successful production of antibody fragments, the lack of direction/guidance presented in the specification regarding same, the lack

of working examples, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claim 12 recites the limitation "the binding pocket" in line 4. There is insufficient antecedent basis for this limitation in the claim.

16. Claim 12 recites "one polypeptide consisting of a portion of a human IgG **heavy chain** starting at one of amino acids 106 to 128 and ending at one of amino acids 215 to 225 of human IgG **light chain** as set forth in SEQ ID NO:2" (see the last three lines of the claim; emphasis added). The claim is indefinite because it first indicates that the polypeptide is a portion of a heavy chain, then indicates to the contrary that it is part of a light chain.

17. Claims 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that the two polypeptides in the composite polypeptide composition are *bound to each other* as a heterodimer.

The specification discloses that the claimed screening methods are designed to identify chemical entities that associate with Fab fragments via a binding pocket that is formed at the

interface of a light chain and a heavy chain, and in particular in the constant regions of these domains (CL and CH1 regions, respectively). See, e.g., the abstract. Therefore, the binding pocket is formed when the heavy and light chains associate with each other in the tertiary structure of a fully folded Fab fragment.

However, the instant claims do not require any association between the two polypeptide chains, and would therefore encompass compositions in which the two chains are not bound to each other. Such compositions would not contain the disclosed binding pocket. Since the claimed methods involve screening potential ligands for binding to this binding pocket as disclosed, it is essential to the performance of the method that the binding pocket be present in the composition—i.e., that the two polypeptides be bound to each other.

18. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step in which affinities of the entities are measured.

Claim 13 requires "grading said entities according to affinity". However, the claims fail to recite any steps in which the affinities of the entities are actually measured or calculated. It is also suggested that the claim make clear what affinity is being invoked--i.e., the affinity of the entities for the composition, if this is Applicant's intended meaning.

Conclusion

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

20. Schoonjans et al. (US 6,809,185 B1) is cited as being cumulative to the non-patent literature publication by Schoonjans et al. discussed above.

21. Padlan et al. ("Antibody Fab assembly: the interface residues between CH1 and CL" Mol Immunol. 1986 Sep;23(9):951-60) teaches a cavity at the interface of the CH1 and CL constant domains (see especially pages 955 and 959).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:00-2:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641